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STATE-OF-THE-ART PAPER

Assessing Low Levels of High-Density Lipoprotein Cholesterol as a Risk Factor in Coronary Heart Disease

A Working Group Report and Update

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Clinical data show that a 1% increase in serum concentrations of high-density lipoprotein cholesterol (HDL-C) can decrease cardiovascular risk by 2% to 3%. Therefore, mechanisms affecting the level and functionality of high-density lipoprotein (HDL) and its constituents are being investigated as targets for the rational development of drugs to prevent or treat cardiovascular disease. High-density lipoprotein-related research may also increase our understanding of the link between atherosclerosis and metabolic disorders. This report and update of the HDL Working Group discusses HDL metabolism and reverse cholesterol transport, impaired HDL as a marker and a cause of proatherogenic states, and experimental and current approaches to HDL-related therapy. (J Am Coll Cardiol 2004;43:717–24)

On January 12 to 13, 2001, a distinguished international group of 25 investigators with expertise in epidemiology, endocrinology, molecular biology, public health, lipid metabolism, cardiovascular medicine, and preventive cardiology (Appendix) met in Scottsdale, Arizona, to discuss the latest research on low levels of high-density lipoprotein cholesterol (HDL-C) as a risk factor for coronary heart disease (CHD). It was the second meeting of a working group formed one year earlier to focus the attention of the medical community on this issue. This article summarizes the 2001 meeting and provides further information from recently published research.

The Working Group reached agreement on several points (Table 1), most importantly, that: 1) raising HDL-C levels is useful in atheroprevention, in addition to reducing low-density lipoprotein cholesterol (LDL-C) levels, and 2) further basic and clinical research is essential in order to improve our ability to raise high-density lipoprotein (HDL) levels.

HDL METABOLISM

Transport rate and fractional catabolic rate. Apolipoprotein (apo) A-I and apo A-II are the two major protein components of HDL. In the general population, an inverse relation between CHD and plasma levels of apo A-I has been demonstrated. However, an association between CHD risk and apo A-II levels has not been clearly shown, and the role of apo A-II in atherogenesis is not well defined (1). Therefore, the following discussion will focus primarily on HDL and apo A-I.

Turnover studies indicate that HDL-C levels are determined by the fractional catabolic rate (FCR) of apo A-I and apo A-II (2–4). The transport rate (TR) of apo A-I and apo A-II generally plays a less important role in regulating HDL-C levels (2,5), except in certain circumstances (such as intake of ethanol and saturated fat) (6,7).

The apo A-I FCR is largely a function of HDL lipid content (and, therefore, size). Consequently, plasma factors that participate in the remodeling of HDL particles are crucial. These include lipid transfer proteins (e.g., cholesteryl ester transfer protein [CETP]) and the enzymes lecithin:cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL), and hepatic lipase (HL) (Fig. 1) (8). Lecithin: cholesterol acyltransferase and lipoprotein lipase are major factors in the production of HDL, whereas CETP and HL are involved in its catabolism.

The efflux of free cholesterol from peripheral cells is another major factor regulating HDL lipid content, size, FCR, and plasma level. This is the first step in reverse cholesterol transport (RCT), the process whereby HDL transports cholesterol to the liver for biliary excretion. Free cholesterol is taken up by small lipid-poor apo A-I particles ("nascent" HDL), which are secreted in the liver and are highly efficient acceptors of cell membrane lipids.

Cellular cholesterol efflux is mediated by the ABC-A1 regulatory protein (9). Mutations in the ABC-A1 gene prevent cholesterol efflux, leading to a rapid clearance of small lipid-poor apo A-I from plasma and sterol deposition in macrophages (10,11). Heterozygotes can have hypoalphalipoproteinemia; homozygotes or compound heterozygotes have Tangier disease (TD), with severe decreases in HDL size, lipidation, and levels, and hypercatabolism of apo A-I (10–12). Interestingly, very small dense lipid-poor HDL particles may play a dual role in regulating HDL concentration (13). Nascent particles are crucial to extracellular HDL maturation; however, "senescent" HDL particles

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Abbreviations and Acronyms

ABC-A1 = adenosine triphosphate binding cassette-A1
apo = apolipoprotein
CETP = cholesteryl ester transfer protein
CHD = coronary heart disease
FCR = fractional catabolic rate
HDL-C = high-density lipoprotein cholesterol
HL = hepatic lipase
LCAT = lecithin:cholesterol acyltransferase
LDL-C = low-density lipoprotein cholesterol
PPAR = peroxisome proliferator activated receptor
RCT = reverse cholesterol transport
SR-B1 = scavenger receptor B1
VLDL = very low-density lipoprotein

generated by the actions of lipid transfer proteins or endothelial lipases are highly susceptible to renal glomerular filtration (Fig. 1), which increases the FCR of apo A-1 and may lead to low levels of HDL-C and apo A-1 (13).

Hypertriglyceridemia is strongly associated with low HDL-C levels (14), and the FCR of apo A-I is elevated in patients with this combined lipid abnormality. Even when triglycerides are normal, however, persons with low HDL-C tend to have small HDL-C particles and elevated FCR (3), perhaps resulting from lipase overactivity independent of a primary increase in triglycerides (14).

Niacin (nicotinic acid), probably the most effective HDL-C–raising agent, decreases the FCR of apo A-I (15). In contrast, fibrates, statins, and oral estrogen raise HDL-C levels by increasing the TR (16–18). Ethanol also raises HDL levels by increasing the TR of apo AI (6); however, the risks associated with promoting alcohol consumption are generally considered to make this an inadvisable HDL-raising strategy. Some believe that grapeseed oil has an HDL-raising effect, but there is a lack of scientific evidence to support this.

Table 1. HDL as a Therapeutic Target: HDL Working Group Consensus

- HDL and its constituents are rational targets of cardiovascular therapy.
- HDL appears to have several atheroprotective properties, although RCT may be the primary mechanism.
- Impaired HDL is a cause and a marker of proatherogenic states.
- Promising experimental approaches that may maximize the atheroprotective activity of HDL-C include:
  - stimulating apo A-I production, which may promote RCT
  - targeting other mechanisms related to RCT
  - targeting the metabolic syndrome
  - targeting other antiatherogenic properties of HDL
  - slowing HDL or apo A-I turnover
- Methods must be developed to measure the rates of cholesterol efflux and RCT.
- HDL-C–related interventions, both lifestyle and pharmacologic, should be used in conjunction with strategies aimed at modifying other lipid abnormalities (e.g., LDL-C, triglycerides).
- Optimal HDL-C–raising benefit may be derived from combination therapy in some patients.
- Continued basic research is essential in order to identify molecular targets for future drug development.

apo = apolipoprotein; HDL-C= high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RCT = reverse cholesterol transport.

Reverse cholesterol transport. The reverse cholesterol transport begins with the uptake of cholesterol from peripheral cells, perhaps especially arterial wall macrophages, by nascent HDL. These particles are remodeled into mature HDL_2 through the activity of LCAT, which catalyzes the esterification of cholesterol, and LPL, which hydrolyzes triglycerides in circulating lipoproteins, generating surface components that contribute to HDL enlargement (3,19). Cholesteryl ester transfer protein then mediates the delivery of much of the esterified HDL cholesterol to apo-B–containing lipoproteins in exchange for triglycerides (Fig. 1) (20).

The HDL particles generated by CETP-mediated activity are enriched in triglycerides relative to their cholesteryl ester content (21). Following HL-mediated hydrolysis of the triglyceride component, the cholesteryl esters undergo clearance by the SR-B1 receptor (22). This process is termed "direct" RCT, because the cholesterol has been associated with the HDL since its initial uptake from peripheral cells (22). The SR-B1 clearance results in lipid-depleted HDL particles that may be susceptible to enhanced glomerular filtration, as well as catabolism by other tissues (13,23). This accounts for a substantial portion of apo A-I catabolism. Paradoxically, oral estrogen appears to suppress HL activity without a corresponding decrease in the FCR of apo A-I or apo A-II (18).

Niacin decreases the FCR of apo A-I, reportedly by selectively reducing hepatic uptake of HDL apo A-I without impairing hepatic uptake of HDL cholesteryl esters. The resulting increase in levels of apo A-I containing HDL particles augments RCT by promoting apo A-I–mediated cellular cholesterol efflux (15).

A major advance in our understanding of cholesterol metabolism has been the recognition of a second major pathway involved in the return of cholesterol to the liver. Cholesteryl ester transfer protein transfers much of the HDL cholesteryl esters to very low-density lipoprotein (VLDL) or LDL particles. The esterified cholesterol is transported by these particles (or their remnant lipoproteins) to the liver, where they are taken up by the LDL receptor in a process known as "indirect" RCT (22).

Our understanding of RCT has also been enhanced by the study of the ABC-A1 transporter and TD. Research in transgenic mice found that overexpression of human ABC-A1 led to marked increases in apo A-I and HDL-C levels and to significantly lower aortic atherosclerosis (24). However, another transgenic mouse study involving ABC-A1 overexpression found increased cholesterol efflux without a corresponding rise in HDL level, possibly because of a compensatory downstream increase in HDL catabolism (25). This illustrates the complexity of RCT.

A related lipid transporter, ABC-G1, is up-regulated by cholesterol in macrophages and may provide a compensatory route of residual cholesterol and phospholipid efflux in TD patients (26). Paradoxically, however, a transgenic mouse study reported that overexpression of human ABC-G1 in the liver led to decreased plasma HDL-C and apo A-I levels (27). The

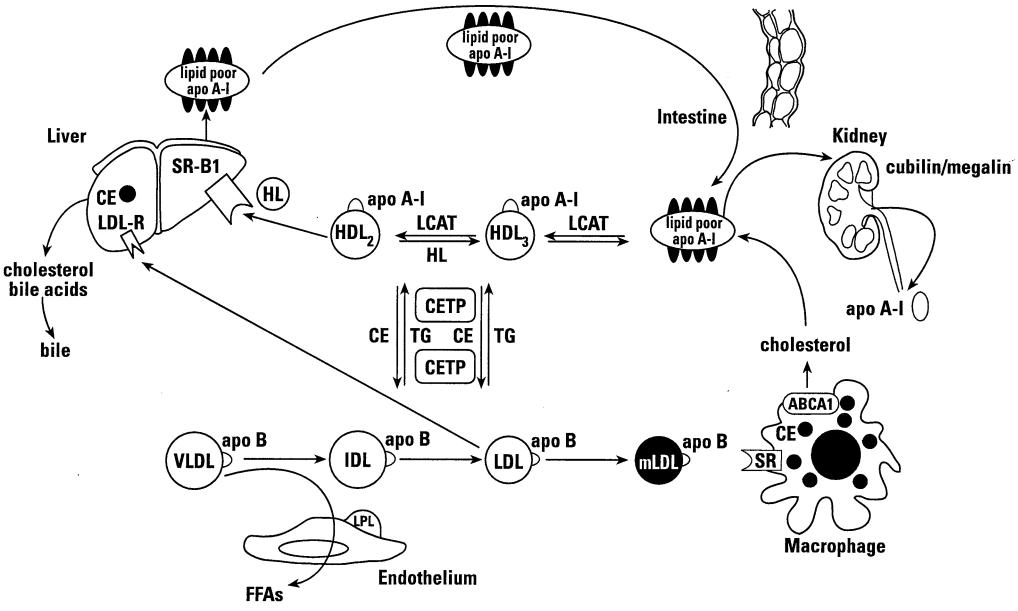

Figure 1. This figure illustrates reverse cholesterol transport, which delivers cholesterol from peripheral cells to the liver for excretion in the bile. The adenosine triphosphate binding cassette (ABC)-A1 transporter mediates the efflux of free cholesterol from peripheral cells, notably macrophages, to apolipoprotein (apo) A-I–rich nascent high-density lipoprotein (HDL). Esterification by lecithin:cholesterol acyltransferase (LCAT) results in the formation of mature spherical HDL_2 particles. Following cholesteryl ester transfer protein (CETP)-mediated exchange of cholesteryl esters (CE) for triglycerides, the latter are hydrolyzed by hepatic lipase (HL). The CE still associated with HDL_2 are then selectively removed from plasma by the scavenger receptor B1 (SR-B1) in the liver ("direct" reverse cholesterol transport [RCT]), resulting in small, lipid-poor apo A-I particles (senescent HDL) that are susceptible to glomerular filtration and endocytosis by the cubilin/megalin receptors in the renal proximal tubule. A portion of the CE transferred to apo-B–containing particles (very low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL], low-density lipoprotein [LDL]) are transported to the liver for uptake by the LDL receptor ("indirect" RCT). Courtesy of Craig T. Basson, MD, PhD, and Carl J. Vaughan, MD, MRCPI. Reprinted with permission. LDL-R = low-density lipoprotein receptor; LPL = lipoprotein lipase; mLDL = modified low-density lipoprotein.

mechanism for this effect is unclear, because there was no up-regulation of the SR-B1 receptor, believed to be the main acceptor of cholesteryl ester in the liver (28), or of cubilin, which mediates endocytosis of apo A-I in the kidney.

Plasma factors. Forty percent to 60% of the interindividual variation in human serum HDL-C concentrations is controlled at the genetic level, and the strong positive correlation between plasma levels of apo A-I and HDL-C suggests that mutant apo A-I genes may be linked to variability in HDL-C levels (29). More than 40 naturally occurring human apo A-I coding-sequence mutations have been identified, of which roughly half are linked to below-average plasma concentrations of HDL apo A-I (30). Among these, deletion of repeats 6 or 7 (residues 143 to 186) dramatically decreases the ability of LCAT, for which apo A-I is a co-factor, to catalyze the esterification of cholesterol. This blocks the maturation of nascent HDL, resulting in hypercatabolism of lipid-poor apo A-I and lower HDL levels (30).

Genetic polymorphisms in plasma factors active in HDL metabolism may help predict response to lipid-modifying therapy. In one study, a C→T substitution at position −514 in the promoter region of the HL gene was associated with decreased benefit in patients treated with lovastatin or niacin. Compared with the TT genotype, patients with the CC polymorphism had a greater decrease in HL activity, greater increase in LDL buoyancy, normalization of HDL_2-C levels, and improvements in LDL-C and apo B levels and in coronary stenosis (31). Clinical end points were not evaluated.

In the Regression Growth Evaluation Statin Study (REGRESS), the TaqIB polymorphism of the CETP gene (designated as B1) was associated both with progression of coronary atherosclerosis and angiographic response to statin therapy. Placebo-treated carriers of the B1/B1 genotype had the greatest disease progression, as measured by change in lumen diameter, compared with B2/B2 (denoting absence of the variant) and B1/B2 carriers. This relation was independent of HDL-C levels, although B1/B1 subjects had higher CETP and lower HDL-C concentrations at baseline compared with B2/B2 subjects. In addition, pravastatin slowed atherosclerosis progression significantly in B1/B1 and B1/B2 carriers versus placebo, whereas B2/B2 carriers experienced no treatment benefit (32). This study did not examine clinical end points. However, plaque size may not be an appropriate surrogate for clinical benefit, because acute coronary syndromes appear to result largely from vulnerable plaques that are only mildly or moderately obstructive (33).

LOW HDL-C: CAUSE OR MARKER OF PROATHEROGENIC STATES?

Low HDL-C levels may directly promote atherogenesis, particularly when there is some elevation in LDL-C; often occur in the presence of increased concentrations of atherogenic lipoproteins (e.g., triglyceride-rich VLDL remnants, small LDL particles); and are often part of the metabolic syndrome, a constellation of lipid, nonlipid (e.g., hypertension,

impaired fasting glucose), and emerging (e.g., prothrombotic/proinflammatory states) risk factors. Under certain conditions, such as the presence of infection, the roles of HDL-C as marker and causative agent may be intertwined.

During the acute-phase response, HDL levels decrease and HDL metabolism is altered (34,35). For example, in a rabbit model, levels of serum amyloid A (SAA), whose synthesis in the liver is largely regulated by acute-phase reactants (cytokines), were shown to increase 60-fold during an inflammatory stress, while levels of apo A-I declined. There was also a marked decrease in the activity of enzymes that render HDL protective against LDL oxidation, with a parallel loss of HDL antioxidant activity (36). An accompanying study found that human acute-phase HDL had elevated SAA content and 58% lower apo A-I content, and promoted (rather than prevented) LDL oxidation in human aortic endothelial cell and smooth muscle cell coculture (36). Thus, infection or inflammation appears to cause proatherogenic changes in both concentration and function of HDL.

HDL-C AS A THERAPEUTIC TARGET IN MANAGING CHD

Not only are low HDL-C concentrations often found in patients with CHD (37), but genetic syndromes of high HDL-C have been linked to longevity and a rare occurrence of premature cardiac events (38).

Experimental approaches to HDL-related therapy. Experimental evidence suggests that augmenting HDL and/or its apolipoproteins can have important vasoprotective effects (39). However, precise methods for measuring the rates of cholesterol efflux and RCT must be developed to evaluate any strategy aimed at stimulating RCT. The following experimental approaches seem to offer promise (Table 1).

STIMULATING APO A-I PRODUCTION. Heightened production of apo A-I may increase the quantity of acceptors available for cholesterol removal from cells. It may also stimulate LCAT, which could promote cellular cholesterol efflux and enhance the efficiency of RCT (26). In transgenic rabbits, overexpression of human apo A-I was shown to increase HDL-C levels two-fold and inhibit the development of atherosclerosis (40).

In a recent phase II study (N = 57), weekly intravenous infusion of recombinant apo A-I Milano (ETC-216) begun within two weeks of an acute coronary event and administered for five weeks led to a significant reduction in atheroma (plaque) volume, as measured by intravascular ultrasound, compared with baseline. It should be noted, however, that the change in the treated group did not differ significantly from that in placebo. For this and other reasons, this novel treatment requires further study in larger trials with clinical end points (42).

Although macrophages do not secrete apo A-I, the ability of extracellular apo A-I to promote cellular cholesterol efflux suggests that the induction of apo A-I expression in macrophages may achieve a similar effect. In one study of apo A-I$^{-/-}$ transgenic mice, macrophage-specific expression of human apo A-I reduced diet-induced arterial lesions, substituting for the antiatherogenic effects of macrophage-derived apo E. This indicates that gene therapy using macrophages to target the artery wall may have promise (43).

Apo A-I and apo A-II gene induction is mediated by peroxisome proliferator-activated receptors (PPARs). Constituting a nuclear receptor subfamily, PPARs are ligand-activated transcription factors that regulate a wide range of genes either directly, by binding to peroxisome proliferator response elements within the gene, or indirectly, by interacting with other transcription-factor pathways (44,45). PPAR-alpha is highly expressed in liver, muscle, kidney, and heart tissue and is primarily involved in lipid metabolism (45,46). PPAR-gamma, predominantly expressed in the intestine and adipose tissue, primarily regulates insulin and glucose metabolism, but also affects lipid metabolism (47,48). Both are present in monocyte/macrophages, endothelial cells, and smooth muscle cells in the vascular wall (45), and both may induce expression of the ABC-A1 gene, which is found in human monocyte/macrophages and macrophage foam cells (48). Fatty acids and their derivatives are natural PPAR ligands, whereas fibrates, statins, and thiazolidinediones (glitazones) are synthetic PPAR activators (16,49,50).

In patients with hypertriglyceridemia, combined hyperlipidemia, or hypercholesterolemia, fibrates raise HDL-C levels by roughly 10% to 15%, at least in part through induction of the apo A-I and apo A-II genes via activation of PPAR-alpha (46). Recently, statins were also shown to activate PPAR-alpha, and a statin response element in the apo A-I gene was identified in the same region as the peroxisome proliferator response elements that confers responsiveness to fibrates (49).

TARGETING OTHER RCT-RELATED MECHANISMS. The scavenger receptor is another potential therapeutic target. Overexpression of hepatic SR-B1 in animals can reduce atherosclerosis while paradoxically lowering plasma HDL-C concentrations, perhaps by stimulating the rate of RCT (51). Efforts to increase HDL levels by inhibiting CETP pose a quandary, because CETP appears to have both proatherogenic and antiatherogenic properties. It may be proatherogenic by mediating the transfer of esterified cholesterol from HDL to apo-B–containing lipoproteins, thereby decreasing HDL-C and raising VLDL-C and LDL-C levels. However, the esterified cholesterol transferred to apo-B-containing particles is transported to the liver, where it is removed from plasma by the LDL receptor. This suggests an antiatherogenic effect. Experts are investigating whether CETP activity can be limited in a way that will not be negated by a decrease in RCT. In rabbit models, a vaccine that elicits CETP antibodies and a CETP inhibitor were shown to raise HDL-C levels and decrease the size of atherosclerotic lesions compared with controls (52,53). Trials of CETP inhibitors have recently begun in humans.

In Asian and Caucasian populations, more than 10 allelic variants of mutations and polymorphisms in the coding region of the CETP gene have been identified. These include the TaqIB (discussed earlier), I405V, and D442G polymorphisms (54). The D442G polymorphism is the most common and has been linked to a CETP deficiency. Found only in Asian populations, it is associated with an increased risk for CHD in subjects with relatively low HDL-C levels (<45 mg/dl), but not in those with HDL-C levels >60 mg/dl. Other research has demonstrated that low CETP activity associated with the I405V polymorphism, which occurs in Asian and Caucasian populations, confers increased vascular risk in the presence of hypertriglyceridemia. Such data suggest that a patient's metabolic status may influence the effect of CETP on atherosclerosis (54). If substantiated, this could have implications for the development of CETP-based therapies.

TARGETING THE METABOLIC SYNDROME. The metabolic syndrome, which increases the risk for CHD at any LDL-C level, is associated with low HDL-C, elevated TG, insulin resistance, abdominal obesity, and physical inactivity (55); it may also lead to type 2 diabetes. Recently recognized as an important endocrine organ, adipose tissue secretes a number of factors (adipokines) that regulate, directly or indirectly, processes (such as insulin resistance) that promote atherogenesis (56,57). In addition, a strong correlation has been shown between intra-abdominal fat and the FCR of Lp-AI, the apo A-I–containing subfraction of HDL. One possible explanation for this effect is that intra-abdominal adipocytes release excess free (unesterified) fatty acids. Hepatic exposure to this excess may lead directly or indirectly to hypercatabolism of apo A-I mediated by the plasma factors described earlier (58).

Thiazolidinediones are insulin sensitizers indicated for type 2 diabetes. They also appear to be useful in the metabolic syndrome (59). As synthetic ligands of PPAR-gamma, thiazolidinediones reduce free fatty acid levels (60), probably by enhancing adipogenesis and/or lowering rates of lipolysis in adipocytes (50). This diminishes the amount of substrate available for triglyceride production in the liver, leading to a decrease in triglyceride levels and thus possibly contributing to elevated HDL-C concentrations. PPAR-gamma activation may also induce expression of the ABC-A1 transporter gene via enhanced expression of the liver-x-receptor co-factor, which may help explain the increase in HDL levels with thiazolidinedione use (45,61).

TARGETING OTHER ANTIATHEROGENIC PROPERTIES OF HDL. The benefit of some therapies may arise from changes in the functionality or concentrations of HDL constituents or subclasses, rather than from changes in total plasma HDL-C levels (62). For example, the HDL-associated protein apo E has antioxidant properties (63,64) that may inhibit oxidative modification of LDL. Other forms of atheroprotection that may relate to HDL subspecies or components include inhibition of endothelial adhesion molecule expression, anticoagulant activity, prostacyclin stabilization, and activation of endothelial nitric oxide synthase, which may promote vasodilation (61).

SLOWING HDL OR APO A-I TURNOVER. Renal degradation of HDL/lipid-poor apo A-I takes place in the proximal renal tubule via cubilin/megalin endocytosis of particles that have been filtered across the glomerulus. Because filtered apo A-I particles cannot return to the plasma, cubilin/megalin does not play a role in determining their rate of catabolism. Instead, a principal determining factor is likely the glomerular filtration rate of the HDL/apo-A-I particles, as regulated by their physicochemical properties (size, shape, charge) (23). Smaller HDL particles and/or lipid-poor/lipid-free apo A-I dissociated from HDL are available for rapid clearance via glomerular filtration (13,23). Consequently, inhibition of HDL remodeling to smaller particles may reduce HDL catabolism and raise HDL levels.

Clinical approaches to HDL-C–related therapy. BENEFITS OF RAISING HDL-C LEVELS: CLINICAL TRIAL EVIDENCE. Epidemiologic data indicate that a 1 mg/dl increase in HDL-C levels is associated with a 2% to 3% reduction in CHD risk, independent of LDL-C levels (65). Thus, even modest increments in HDL-C concentrations appear to be clinically important.

In a study comparing extended release niacin versus gemfibrozil, significant increases of 25% versus 13% in HDL-C levels and 10% versus 2.5% in apo A-I levels were reported (66). Associated in vitro analyses suggest that niacin may selectively inhibit the hepatic uptake of Lp-AI, as discussed earlier, thereby raising concentrations of the HDL Lp-AI subfraction. This may facilitate more efficient RCT by promoting cellular cholesterol efflux (15), which would be consistent with reductions in cardiovascular outcomes seen in other niacin trials (67–69).

Conducted between 1966 and 1975, the Coronary Drug Project found that niacin significantly reduced the incidence of nonfatal myocardial infarction compared with placebo. Although a trend toward decreased mortality was not significant, a follow-up conducted in 1981 reported a significant 11% reduction in mortality in the niacin-treated patients. One possible explanation for this late benefit is that the early decrease in nonfatal myocardial infarction may have translated into a long-term effect on mortality (67).

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), lovastatin in patients with below-average HDL-C and average LDL-C levels increased HDL-C concentrations by 6%. LDL-C and triglyceride levels decreased by 25% and 15%, respectively (70). Participants experienced a 37% reduction in risk for a major coronary event, with the greatest reductions (45% and 44%) occurring in patients in the lower two tertiles of baseline HDL-C (71). Just 17% of the patients in this study would have been eligible for lipid-lowering therapy based on the National Cholesterol Education Program (NCEP) guidelines in effect at the time, which underscores the importance of raising HDL-C levels in

patients whose LDL-C levels may not be considered high. The AFCAPS/TexCAPS and the Lipoprotein and Coronary Atherosclerosis Study, an atherosclerosis regression trial, indicate that patients with low HDL-C levels may be especially responsive to treatment with lovastatin or fluvastatin, respectively (70,72).

Statins may differ in their effects on HDL-C. In one 12-week study comparing rosuvastatin 5 mg and 10 mg with atorvastatin 10 mg, rosuvastatin produced significantly greater increases in HDL (+13% and +12%, respectively) and apo A-I than did atorvastatin 10 mg (+8%) (73). Experimental studies are beginning to explore the nature and mechanisms of these differences among statins.

In selected patients, combination therapy may be considered. The HDL Atherosclerosis Treatment Study (HATS) found that niacin plus simvastatin lowered the risk for major coronary events by 60% to 90% in patients with coronary artery disease, moderately elevated LDL-C levels, and HDL-C levels ≤35 mg/dl (men) or ≤40 mg/dl (women) (69). This was accompanied by regression of stenosis, rather than slowed progression. Overall, HDL levels increased by 26% and Lp-AI levels rose by 81%. In a double-blind dose-ranging study, a formulation containing niacin extended release 2,000 mg and lovastatin 40 mg improved overall lipoprotein profiles, including a 30% increase in HDL-C levels, compared with niacin extended release 1,000 mg/lovastatin 40 mg or lovastatin 40 mg. These results suggest a possible additive effect on CHD risk reduction (74).

In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (75), gemfibrozil did not decrease LDL-C levels in men with CHD and low HDL-C concentrations. However, HDL-C levels rose by 6% (along with a reduction in triglyceride levels) compared with baseline. Although this was accompanied by a 22% decrease in the incidence of coronary events, regression analyses indicate that lipid concentrations accounted for only part of the benefit achieved with drug therapy (76).

Some studies indicate that alpha-blockers for the treatment of hypertension can raise HDL-C levels and improve other lipid subfractions. In one 22-week randomized trial involving 45 men with central obesity, doxazosin significantly increased HDL-C levels and lowered triglycerides compared with atenolol, a beta-blocker (77). A meta-analysis of 22 randomized controlled trials also found that alpha-blockers favorably modified HDL-C levels when compared with placebo or other antihypertensive regimens (78). Doxazosin appears to increase insulin sensitivity and improve insulin resistance as well (78,79). In the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT), the risk for fatal CHD/nonfatal myocardial infarction was equal with doxazosin and chlorthalidone. However, the doxazosin-treated patients had significantly higher rates of combined CHD and cardiovascular events, which led investigators to discontinue this arm of the trial. At baseline, mean HDL-C levels were 47 mg/dl in both treatment groups, and 12% of the participants had HDL-C levels <35 mg/dl (80).

NCEP GUIDELINES. As in previous NCEP guidelines for detecting, evaluating, and treating high blood cholesterol, the 2001 recommendations identify LDL-C reduction as the primary goal of risk-reduction therapy (55).

In intermediate-risk patients, an HDL-C level <40 mg/dl is one of several major risk factors that help determine the LDL-C goal and predict the 10-year risk for CHD. The guidelines also discuss HDL-C in relation to the metabolic syndrome, which is clinically characterized by any three of the following: abdominal obesity, elevated TG levels, low HDL-C levels, elevated blood pressure, and impaired fasting glucose. After LDL-C levels have been lowered, the metabolic syndrome is a potential secondary goal of therapy; it is treated primarily by weight reduction and intensified physical activity. Although low HDL-C levels are considered to be a strong independent predictor of CHD, the guidelines assert that there is insufficient clinical trial evidence to support a therapeutic goal and, moreover, that most currently available lipid-modifying medications have little ability to produce a robust increase in HDL-C levels. Nevertheless, after LDL-C goals have been achieved, the guidelines suggest that niacin or fibrates be considered as treatment for isolated low HDL-C (that is, accompanied by TG levels <200 mg/dl), primarily in patients with established CHD or CHD risk equivalents.

Lifestyle measures, including weight loss and physical activity, are important in raising HDL-C levels. In the case of aerobic exercise, duration appears to be more important than intensity. Omega-3 fatty acids (fish oil), particularly eicosapentaenoic acid and docosahexaenoic acid, may have a modest effect on HDL-C levels (81).

CONCLUSIONS

A growing body of evidence indicates that HDL has an athero-protective effect. Although the 2001 NCEP guidelines state that there is insufficient evidence to support a goal for HDL-C–raising therapy (55), clinical trial results suggest that more frequent and more aggressive treatment of HDL deficiency may be warranted in certain patients.

Consideration of lifestyle measures is always important. In addition, niacin, fibrates, and statins can all raise HDL-C levels. The best choice of medication in low-HDL-C patients varies by individual circumstances.

Reverse cholesterol transport appears to play a large role in the atheroprotective effect of HDL. However, other properties may also contribute to HDL-related cardiovascular risk reduction and constitute potential targets for future drug therapy. In addition, HDL research will likely increase our understanding of the link between atherosclerosis and metabolic disorders.

We expect that the coming decade will bring many new classes of therapies aimed at reducing cardiovascular risk. The Working Group strongly advocates research into

mechanisms of atherogenesis associated with HDL deficiencies. This could lead to the development of drugs that are capable of enhancing HDL-related atheroprotection(41).

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APPENDIX

Assessing HDL-C as a risk factor in coronary heart disease: a Working Group meeting. Chairman: A. M. Gotto, Jr., MD, DPhil. Guest Speakers: H. B. Brewer, Jr., MD; E. A. Brinton, MD; B. G. Brown, MD, PhD; S. M. Grundy, MD, PhD; S. M. Haffner, MD, MPH; M. F. Linton, MD; J. Otvos, PhD; D. J. Rader, MD; M. Sorci-Thomas, PhD; B. Staels, PhD; S. D. Wright, PhD; A. Zambon, MD, PhD.

For a list of the other participants, please see the March 3, 2004, issue of *JACC* at http://www.cardiosource.com/jacc.html.